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AUTHORITY

USAMRMC ltr. 7 Feb 97

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	24 March 1995	annual 1 March 1994 - 28 Feb. 1995

4. TITLE AND SUBTITLE
Drug Evaluation in the Plasmodium falciparum - Aotus Model

5. FUNDING NUMBERS
DAMD17-91-C-1072

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, MD 21702-5012
attn: MCMR-RMI-S

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Distribution limited to U.S. government agencies only; proprietary information, Mar 95.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

A pyrroloquinazoline was toxic to Aotus. Blood induced infections of the AMRU-1 P. vivax strain were not cured with primaquine plus chloroquine. A primaquine analog plus chloroquine cured infections with CQR vivax parasites, indicating in-vivo reversal. The FVO P. falciparum strain was reestablished in Panamanian Aotus to induce immunity acquired by repeated trophozoite challenge. Patent infections were induced in Aotus by Santa Lucia P. falciparum strain trophozoites and sporozoites, a potential model to evaluate DNA vaccines. A DNA plasma vaccine encoded for the P. yoelli CSP gene elicited significant antibodies by intradermal needle injection.

DISTRIBUTION STATEMENT B: Distribution authorized to U.S. Government agencies only [redacted] Other requests for this document shall be referred to PROPRIETARY INFORMATION Mar 95

14. SUBJECT TERMS			15. NUMBER OF PAGES 47 16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Limited

AD_____

CONTRACT NO: DAMD17-91-C-1072

TITLE: Drug Evaluation in the Plasmodium falciparum - Aotus Model

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REPORT DATE:

24 March 1995

TYPE OF REPORT:

ANNUAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick
Frederick, Maryland 21702-5012

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Richard V. Bossart 24 March 1995

PI - Signature Date

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INTRODUCTION

The essence of the problem addressed in this report are: 1) to evaluate the potential antimalarial activity of drugs in the pre-clinical model of Aotus lemurinus lemurinus (Panamanian night monkey) experimentally infected with Plasmodium falciparum or P. vivax, and 2) to use this model to test recombinant DNA malaria vaccines. Drug evaluation studies were supported by the U.S. Army, while the vaccine studies received support from the U. S. Navy Malaria program. Studies with this model were inititated in 1976 at Gorgas Memorial Laboratory, Panama and Development Command. Due to the drug resistance exhibited by the highly pathogenic P. falciparum parasites in Asia, Africa, and Latin America, it is essential that new drugs be evaluated in the preclinical Aotus model for their potential usefulness against human infections.

Initially, antimalarial drug studies used the Colombian Aotus as the experimental host (1,2). In the mid 1970's embargoes imposed by South American countries on the exportation of monkeys seriously restricted the use of Aotus for biomedical research in the United States. Panamanian Aotus were available at Gorgas Memorial Laboratory, Panama, and the project transferred here in 1976. Diverse avenues of research have been pursued in attempts to identify effective new antimalarial drugs. Three strains of P. falciparum, Vietnam Smith, Uganda Palo Alto, and Vietnam Oak Knoll, had been adapted to Panamanian Aotus. These strains exhibit diverse susceptibility and/or resistance to standard antimalarial agents. The course of untreated infections in Panamanian Aotus has been characterized and compared with that in Aotus of Colombia (3). Overall, the virulence of these strains was less in Panamanian than in Colombian owl monkeys, as indicated by lower mortality rates of Panamanian monkeys during the first 30 days of patency. Maximum parasitemias of the Vietnam Smith and Uganda Palo Alto strains were, however, significantly higher during the first 15 days of patency in Panamanian than in Colombian owl monkeys. These quantitative differences in infection parameters between Panamanian and Colombian owl monkeys have not invalidated the use of the former for the evaluation of new antimalarial drugs.

Numerous candidate antimalarial drugs of diverse chemical classes have been evaluated against trophozoite-induced infections of one or more P. falciparum strains during the course of these contracts. In seeking alternatives to primaquine, two 8-aminoquinolines proved to be active against the blood stages of P. falciparum (4,5). Desferrioxamine, an iron-specific chelating agent, was shown to suppress parasitemias of the virulent Uganda Palo Alto strain of P. falciparum (6). The in vitro activity of two

halogenated histidine analogs was not confirmed by evaluation against P. falciparum infections in owl monkeys (7).

Chloroquine-resistance of P. falciparum represents the greatest challenge in developing effective antimalarial drugs. Reversal of chloroquine-resistance in P. falciparum, in vitro, was achieved by the co-administration of verapamil (a calcium channel blocker) plus chloroquine (8). Other in vitro studies have shown that there is a significantly greater efflux of chloroquine from erythrocytes containing falciparum parasites resistant to chloroquine than from red cells parasitized by chloroquine-sensitive falciparum malaria (9). Calcium channel blockers appear to prevent this active efflux of chloroquine, thus allowing the drug to accumulate to parasiticidal levels.

Based upon the success of in vitro reversal of chloroquine-resistance, trials were initiated to determine if resistance could be reversed in Aotus infected with the chloroquine-resistant Vietnam Smith strain of P. falciparum. Six calcium channel blockers, or similarly acting drugs, were co-administered with chloroquine in diverse regimens. The desideratum of chloroquine-resistance reversal was administration of a single course of treatment, with parasite clearance and infection cure. Suppression of parasitemia was obtained during an initial course of treatment, but parasite clearance and cure occurred in some instances only after re-treatment. Such infection parameters were similar to those in monkeys with self-limited infections and cure could be attributed to acquired immunity.

Limited trials with desipramine, Norpramin, a tricyclic psychotropic drug, demonstrated the feasibility of reversing chloroquine-resistance in vivo (10). Parasite clearance was obtained, but the infection was not cured.

Subsequently, in vivo reversal of chloroquine resistance was obtained with combinations of chloroquine plus chlorpromazine or prochlorperazine. Such reversal was exhibited by rapid suppression and clearance of parasitemia, resulting in infection cure without retreatment (11).

Evaluation of two oil-soluble derivatives of artemisinin, artemether and arteether, demonstrates that both possess similar activity to cure infections of a multi-drug resistant P. falciparum strain in Aotus.

Both the purpose and methods of approach of the present work remains essentially unchanged since 1976, viz to ascertain the antimalarial activity of drugs against P. falciparum infections in Aotus. The method of approach may

vary on an ad hoc basis, such as administering a combination of drugs.

The long term goal of the second part of this project is to develop fully protective DNA vaccines that induce protective immune responses against the sporozoite, liver and erythrocytic stages of P. falciparum. If successful, it will establish for the first time that DNA vaccines can protect non-human primates, a critical step toward using DNA vaccines in humans.

Vaccines are aimed at inducing immune responses that disrupt the complex cycle of the parasite at one more points: anti-sporozoite antibodies that prevent invasion of hepatocytes; cytotoxic T lymphocytes, cytokines, and antibodies that eliminate infected hepatocytes; antimerozoite antibodies that prevent invasion of erythrocytes; antibodies that neutralize parasite exoantigens known to induce harmful cytokine responses; antibodies that attack infected erythrocytes; cytokines that kill parasites within erythrocytes; and, anti-sexual stage antibodies that prevent the development of sporozoites in the mosquito.

Previous trials of malaria blood stage vaccines have shown that the Panamanian Aotus P. falciparum model to be suitable for this purpose. (12, 13, 14)

BODY

I. Experimental Methods

The first intent of this project is to evaluate the potential antimalarial activity of drugs, or combination thereof, in the preclinical model of Aotus experimentally infected with P. falciparum (or P. vivax). Specifically, the vertebrate host is Aotus lemurinus lemurinus, the Panamanian night monkey. These animals are either feral, laboratory adapted or laboratory born. No naturally acquired, human plasmodium infection has been reported in Aotus. The Vietnam Smith/RE strain of P. falciparum was adapted to Aotus of Colombian origin in 1971 (1) and in Panamanian Aotus in 1976. (3) The course of untreated infections, essential for comparison with treated infections, has been documented in Panamanian Aotus (3). This plasmodium strain is resistant to maximally tolerated doses of chloroquine, pyrimethamine, and quinine (2).

To initiate an experiment, infected blood (with 2.5% sodium citrate as the anticoagulant) from an untreated Aotus was diluted appropriately in chilled saline (0.85%), such that each milliliter contained 5,000,000 parasites. This amount was inoculated into the saphenous vein of experimental and control monkeys.

Blood films, prepared and examined daily beginning on the first post-inoculation day, were stained with Giemsa. Parasitemias were evaluated as follows: negative, if no parasites were detected on a thick blood film after examination for at least 5 minutes; <10 parasites per cmm, if positive only on the thick blood film; parasite enumeration was by the Earle-Perez method and reported as the number of parasites per cmm. (15)

Blood films from untreated Aotus, serving as passage and/or control subjects, were prepared and examined daily during the primary patent period, and daily thereafter for at least three consecutive days after parasites could last be detected on thick blood films. When parasitemia had cleared, films were made and examined twice weekly until a total of 100 negative days had been recorded. If recrudescence occurred, blood films were obtained again on a daily basis.

Parasitemias were evaluated daily during the treatment period and until blood films were negative for at least seven consecutive days. The frequency of smearing was then reduced to two times per week (Monday and Thursdays or Tuesdays and Fridays). If no recrudescences occurred during a 100 day examination period, the infection was considered to have been cured.

Drug doses were calculated as mg base per kg of body weight. Stock solutions of water soluble compounds, at appropriate concentrations, were prepared with distilled water and stored at 8 C for the treatment period. If a compound was water insoluble, a suspension of the requisite amount of drug was prepared daily with 0.3% methylcellulose (in distilled water).

Oral administration of drugs was by gastric intubation with a 14 French catheter. The total volume of fluid administered, drug solution or suspension, and rinse was 14 ml.

The second intent of this project is to ultimately evaluate recombinant vaccines against the blood and sporozoite stages of P. falciparum and against the blood stages of P. vivax in the Panamanian Aotus model. Prior to actual anti-parasitic experiments various routes of administration of a candidate vaccine must be tried so as to produce sugnificant antibody levels. These trials will be deailed in the approprite sections, as will other experiments associated with the Navy Malaria program.

II. Results

A. Toxicity of WR 227825AD (BH 35430)

This drug, a pyrroloquinazoline, was effective in the murine malaria model. Before initiating antimalarial studies in the Aotus - falciparum model, the overt toxicity of WR 227825 was examined in monkeys cured of malaria infections as follows:

NM 12625 4.0 mg/kg, (oral), twice daily for 3 days. The animal died 6 days after termination of treatment,

exhibiting anorexia, dehydration, and a 19% loss of bodyweight.

NM 11614 (splenectomized)
NM 12228

Each of these animals was administered an oral dose of 1.0 mg/kg, twice daily, for 3 days. NM 11614 died on day 6 post treatment, with a 21% body weight loss. NM 1228 also died on the 6th day after treatment, with a 20% loss of body weight.

The last experiment in this series further reduced the drug dose, administered to one monkey, and in a second monkey, the experimental drug was co-administered with WR 139004AC (BK 64208), folinic acid, in an attempt to prevent toxicity.

11425 WR 227825 0.1 mg/kg (oral), once daily for 3 days

12531 WR 227825 as above plus folinic acid 1.0 mg/kg (oral), once daily for 3 days.

Both animals survived without significant weight loss. Since a total dose of 0.3 mg/kg of WR 227825 was not toxic, then it remains to be proven if folinic acid will obviate toxicity when co-administered at a known toxic dose of the pyrroloquinazoline.

B. WR 238605AJ (BM 12562)

As detailed in the previous annual report, the AMRU-1 strain of Plasmodium vivax was adapted to Panamanian Aotus, and the strain RIII resistance to chloroquine confirmed. Evaluation of WR 238605, a primaquine analog, at the Army Medical Research Unit, Ingleburn, Australia, showed that a dose of 3 mg/kg x 3 days cured infections in 2 of 3 Aotus, and that a dose of 12 mg/kg x 3 days cured infections in 3 of 3 Aotus. An experiment was designed to confirm and expand the activity of these doses. Parasitemia responses are detailed in Table 1 and summarized in Table 2. A dose of 1.0 mg/kg x 3 days cleared parasitemias, but with recrudescence. A dose of 3.0 mg/kg x 3 days, administered during the ascending parasitemia and against recurdescences cured infections. The highest dose, 12.0 mg/kg x 3 days, as a primary treatment, cured 3 of 3 infections.

C. WR 238605AJ (BM 12562)
WR 2975AW (BJ 08241), primaquine
WR 1544BM (AR 20613), chloroquine

Having determined that the AMRU-1 strain of P. vivax is resistant to 10.0 mg/kg (x3) of WR 1544 (chloroquine), and that WR 238605 (a primaquine analog) at a dose of 1.0 mg/kg (x3) days will clear parasitemias, but not cure blood-induced infections, a further study was initiated to:

1. Test parasite response to the daily maximum tolerated dose of chloroquine, 20.0 mg/kg.

2. Evaluate WR 238605 at doses lower than 1.0 mg/kg to identify a suppressive only dose.

3. To evaluate WR 2975 (primaquine) against the chloroquine-resistant AMRU-1 strain.

Detailed parasite responses to 20.0 mg/kg (x 3 days) of chloroquine are shown in Table 3 and summarized in Table 4. Parasitemias in 2 of 3 Aotus were cleared, with subsequent recrudescence; parasites were suppressed only in one Aotus.

The data in Tables 5 and 6 show that primary treatment with WR 238605 at doses of 0.11 and 0.33 mg/kg (x 3) had either no effect or a suppressive effect on parasitemia. Primary treatment with this primaquine analog at 1.0 mg/kg (3 days) cleared parasites, without cure, in 3 of 3 Aotus, while retreatment at this dose cured 4 of 5 infections. A dose of 3.0 mg/kg (x 3 days) cured 4 of 4 infections in retreated monkeys.

Parasite response to WR 2975, primaquine, administered at doses ranging from 0.33 to 90.0 mg/kg (x 3 days) are detailed in Table 7 and summarized in Table 8. Primaquine, administered as the primary treatment was first effective at a dose of 10.0 mg/kg (x 3 days) clearing parasitemia, but without infection cure. A primary dose of 30.0 mg/kg (x3 days) cured infections in 2 of 3 Aotus.

The results of this experiment show that: 1) the maximum tolerated dose (20.0 mg/kg x 3 days) clears AMRU-1 (chloroquine resistant parasites, with recrudescence; 2) at a dose of 1.0 mg/kg (x 3 days), WR 238605 only clears infections with this parasite strain; 3) primaquine will clear these P. vivax parasites, at a dose of 10.0 mg/kg (x 3 days), in contrast with WR 238605 which clears only at 1.0 mg/kg (x 3 days).

Based upon these data, an experiment was designed to evaluate the activity of two drug combinations - primaquine plus chloroquine, and WR 238605 plus chloroquine, presented in the succeeding section.

D. WR 1544BM (AR 20613), chloroquine
WR 2975AW (BJ 08241), primaquine
plus WR 1544BM, chloroquine
WR 238605 AJ (BM 12562) plus WR 1544BM, chloroquine

Based upon the demonstration of the in vivo reversal of P. falciparum chloroquine-resistance, we initiated a similar experiment using the chloroquine resistant AMRU-1 strain of P. vivax, chloroquine being administered with either WR 2975 (primaquine) or WR 238605 (a primaquine analog). The initial treatment doses of the two 8-aminoquinolines were selected from results of the preceeding study, while the non-effective 10.0 mg/kg (x 3 days) dose of chloroquine was used.

As shown in Tables 9 and 10, chloroquine (10.0 mg/kg x 3 days) only suppressed parasitemias, a confirmation of previous trials.

The data in Tables 11 and 12 indicate that WR 2975 (primaquine), alone at a dose of 1.0 mg/kg (x 3) had no effect upon the parasites, while this dose plus chloroquine, as a primary treatment only suppressed the parasitemia. Infection cures were obtained but at higher primaquine doses, and after a total of three drug regimens. Infection cure was due substantially to acquired resistance rather than reversal of chloroquine resistance.

WR 238605, administered alone (Tables 13 and 14), at doses of 0.1 and 0.3 mg/kg (x 3 days), had no antimalarial activity. A dose of 1.0 mg/kg (x 3 days) again cleared parasitemia, with recrudescence. Results for the WR 238605 chloroquine combination are detailed and summarized in Tables 15 and 16. Parasitemia suppression occurred when WR 238605 at a dose of 0.1 mg/kg (x 3 days) plus chloroquine was administered as primary treatment and when treatment failures following 0.1 mg/kg (x 3) were retreated with this dose plus chloroquine.

In contrast to no parasitemia response to a dose of 0.3 mg/kg (x 3) of WR 238605 administered during the ascending phase, this dose plus chloroquine cleared (with recrudescence) parasitemias, as did retreatment with the drug combination. Moreover, a single retreatment cured the infection in 1 of 3 monkeys.

Although 1.0 mg/kg (x 3) of WR 238605, alone, has proven to be non curative, this dose plus chloroquine cured infection in 2 of 3 Aotus when administered as the primary treatment. While difficult to separate from in-vivo reversal of chloroquine-resistance and acquired immunity, infections in 12 of 12 Aotus were cured after combined drug retreatment with WR 238605 (1.0 mg/kg x 3 days) plus chloroquine.

There was no evidence of chloroquine-resistance reversal using primaquine-chloroquine, whereas the WR 238605 - chloroquine combination did indicate that such reversal occurred, when the two drugs were administered at doses previously shown to be non-curative.

An overall summary of drug activity against the AMRU-1 strain of P. vivax is presented in Table 17.

E. Establishment of the Plasmodium falciparum (FVO strain) trophozoite model.

Of the various P. falciparum strains adapted to non-human primates, the FVO (Vietnam Oak Knoll) strain would be useful for vaccine studies as only 25-30% of infected Panamanian Aotus self-cure (3). The rest of the infected animals require curative drug treatment or death will ensue. When evaluating a vaccine, the higher the proportion of self-cure, the greater the number of animals needed in each experimental group to assure that the animals are protected by the vaccine and not self curing.

To compare the efficacy of an "artificial" vaccine with protection afforded by acquired immunity, an experiment was initiated to induce immunity by repeated trophozoite

challenge. Briefly, malaria naive Panamanian Aotus were inoculated with 10^4 parasites of the FVO strain, the parasitemia monitored daily by blood film examination, and the infection cured with mefloquine (40.0 mg/kg, oral, x 3 days) when parasitemia approximated 800,000 per cmm. About 4 to 6 weeks after infection cure, the animals will be rechallenged with parasites from a donor monkey whose infection was initiated by cryopreserved parasites. Donor animals, cured of infection, will be recycled ino the challenge group. Challenges will be repeated until the monkeys demonstrate complete immunity.

Results of the first challenge are shown in Table 18. As expected, patency was delayed in the malaria naive monkeys following inoculation of 10^4 blood stage parasites; an inoculum 500 times greater than used in this study will initiate patency on the day following inoculation. Mefloquine treatment was initiated at less than the stipulated parasitemia in order to ensure survival.

A degree of immunity acquired from a previous infection was demonstrated in 12687 and 12727 by a prepatent period longer than in the three malaria naive monkeys.

Aotus 12726, 12730, and 12731, had each been vaccinated (intramuscularly) three times with 2.0 mg of nkCMV/P£ AMA, the last injection being 28 days prior to challenge with FVO parasites. That the vaccine was not protective is shown by prepatent periods equal to those in the malaria naive animals, and the high parasitemias. Despite the intervention of chemotherapy, two of the three vaccinated animals died of overwhelming malaria infections.

F. Establishement of the Plasmodium falciparum (Santa Lucia strain) sporozoite model

In order to test a projected plasmid DNA vaccine against Plasmodium falciparum sporozoites, it is necessary to establish a Panamanian Aotus model. The Santa Lucia strain of P. falciparum was selected because of extensive use of this parasite by Dr. W. Collins, CDC, Atlanta, GA, who has consistently obtained infections induced by sporozoites, albeit in splenectomized Aotus of South American origin. Prior to sporozoite inoculation, a sine qua non of this study was to ascertain if Panamanian Aotus would support trophozoite-induced infections of the Santa Lucia strain.

Approximately, 93 x 10^6 stage parasites were inoculated intravenously into each of two Panamanian Aotus as follows: 17732 (splenectomized) - parasites were detectable on a thick blood film on day 1 post-inoculation, with a patent period of 34 days; the maximum parasitemia of 197,120

per cmm occurred on patent day 26.

12744 (normal) - parasites were first detected on day 6 post-inoculation, followed by a patent period of 13 days, maximum parasitemia of 27° per cmm in patent day 6; after a subpatent period of 23 days, there were 13 days of patency, and a maximum parasitemia of 940 per cmm on patent day 7.

Since data indicate that the blood stages of the Santa Lucia strain will develop in Panamanian Aotus, both normal and splenectomized, Santa Lucia sporozoites were inoculated as follows: each of 12 Aotus were inoculated intravenously with approximately 20,000 sporozoites, and divided into 3 groups of 4 animals. Group 1 subjects had been splenectomized prior to inoculation; monkeys in Group 2 were splenectomized on day 7 post inoculation, and animals in Group 3 are scheduled to be splenectomized 28 days after sporozoite inoculation. In addition to examination of Giemsa stained blood films for parasites, blood is being processed for parasite detection by the PCR technique.

Table 19 shows that, to date, infections are demonstrable by blood films in 2 of 4 monkeys splenectomized prior to inoculation, in 4 of 4 monkeys splenectomized on day 7 post inoculation, and in 2 of 4 still intact animals. Splenectomy was delayed as parasites were observed on days 23, and 25, respectively, 5 and 3 days prior to the scheduled splenectony. These animals will be splenectomized on day 35. post inoculation.

G. Immunogenecity of a DNA vaccine

Using Aotus cured of both P. falciparum and P. vivax infections, a series of experiments dealt with determining the optimal dose, route of delivery, and schedule for a DNA plasmid which encoded the P. yoelli CSP gene. This gene was selected because of its known immunogenicity in mice. In the first experiment with 12 Aotus, the CSP plasmid was injected intramuscularly at doses of 5, 50, and 500 µg of DNA at four week intervals. Sera samples were obtained and immunofluorescene (IFA) assays performed on P. Yoelli sporozoites to determine if antibodies were produced to the CSP protein. Few or no antibodies were detected by IFA.

For the second experiment, the dose was increased, the interval between doses was shortened, and the plasmid injected intramuscularly and intradermally. In some animals, the site of intramuscular injection was pretreated with bupivacaine. A total of 36 monkeys was incorporated into this experiment. Significant antibody titers (as high as 1:2560) were achieved only in the monkeys injected intradermally, without pretreatment. The dose of DNA ranged

from 125 to 2000 µg. These results not only demonstrated the feasibility of producing antibodies in Aotus by a DNA plasmid vaccine, but identified the intradermal route as the site of choice.

In a subsequent experiment, the number of injection sites (1, 2, and 6) to deliver the same amount of antigen were compared. Antibody titers were the highest in monkeys that had been injected six times. If a vaccine proves effective against a human plamodium in the Aotus model, the impracticality of multiple needle intradermal sites for vaccination in humans is obvious. Accordingly, an experiment is in progress in which a newly-developed gene rapidly injects antigen intradermally.

III. Conclusions

WR 227825, a pyrroloquinazoline, was toxic at total doses of 24.0 and 9.0 mg/kg, but not at 0.6 mg/kg. Prior to evaluating this drug as an antimalarial, it must be determined if folinic acid will reverse the drug's toxicity.

Extensive studies with the chloroquine-resistant AMRU-1 strain of P. vivax have shown that: 1) the parasites are resistant to the maximum tolerated daily dose (20.0 mg/kg) of chloroquine; 2) primaquine (WR 2975) alone, cured 2 of 3 trophozoite-induced infections at a dose of 30.0 mg/kg (x 3) when administered during the ascending phase of parasitemia; 3) primaquine (3.0 mg/kg x 3) plus chloroquine (10.0 mg/kg x 3) plus chloroquine (10.0 mg/kg x 3) administered as a primary treatment did not clear parasitemias; 4) WR 238605, a primaquine analog, administered alone at 1.0 mg/kg (x 3) plus chloroquine (10.0 mg/kg x 3), as a primary treatment, cured 1 of 3 infections.

There was no evidence of chloroquine-resistance reversal using primaquine-chloroquine, whereas the WR 238605 - chloroquine combination did indicate that such reversal occurred, when the two drugs were administered at doses previously shown to be non-curative.

The FVO (Vietnam Oak Knoll) strain of P. falciparum was re-established in Panamanian Aotus. This model eventually will be used to evaluate a DNA trophoroite stage vaccine. An experiment was initiated to immunize monkeys against this virulent strain by a repeated challenge cure technique to compare results with those obtained by a vaccine.

To determine the efficacy of a vaccine directed against the hepatic stages of P. falciparum, a sporozoite induced infection model had to be developed. It was initially determined that Panamanian Aotus (splenectomized and intact)

supported the erythrocytic development of the Santa Lucia strain of P. falciparum. Subsequently, and to date, inoculation of Santa Lucia sporozoites have induce patent infections in splenectomized (6 of 8) and in intact (2 of 4) Panamanian Aotus. These results indicate that the model is suitable to test a DNA vaccine designed to prevent development of the exoerythrocytic stages of P. falciparum.

In a series of experiments, it was shown that a DNA plasmid vaccine, encoded for the P. yoelii CSP gene, produced antibodies in Aotus, cured of P. falciparum and P. vivax infections. An extensive study determined that six, intradermal injection sites yielded the highest antibody titers. An additional study is in progress to obviate needle intradermal injections by using a gene gun.

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TABLE 1

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12594	1.0	2	28	22	31	20	4	0.5	0.3	<0.01	<0.01	<0.01
12610	1.0	1	17	12	19	10	1	<0.01	<0.01	<0.01	<0.01	<0.01
12622	1.0	1	15	13	16	13	9	1	<0.01	<0.01	<0.01	<0.01
12595	3.0	0.9	2	4	11	2	0.1	<0.01	<0.01	<0.01	0	0
12609	3.0	1	13	10	13	10	0.4	0.6	<0.01	<0.01	<0.01	<0.01
12615	3.0	1	16	17	17	3	0.3	<0.01	<0.01	<0.01	<0.01	<0.01
12594r	3.0	0.2	0.6	0.6	0.2	<0.01	<0.01	<0.01	0	0	0	0
12610r	3.0	<0.01	0.1	0.3	<0.01	0	0	0	0	0	0	0
12622r	3.0	<0.01	<0.01	0.2	0.1	0.1	<0.01	<0.01	0	0	0	0
12603	12.0	1	11	14	12	3	0.5	<0.01	<0.01	<0.01	<0.01	<0.01
12623	12.0	0.9	9	12	4	0.8	0.3	<0.01	<0.01	<0.01	<0.01	0
12624	12.0	0.9	2	13	4	1	0.01	<0.01	<0.01	<0.01	0	0

TABLE 2

SUMMARY OF THE ACTIVITY OF WR 238605AJ
(BM 12562) AGAINST INFECTIONS OF THE NEW GUINEA AMRU-1
STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12594	1.0			+	11	18	Re-Rx, higher dose
12610	1.0			+	11	25	Re-Rx, higher dose
12622	1.0			+	11	15	Re-Rx, higher dose
12595	3.0			+	9	n.a.	Cured
12609	3.0			+	11	n.a.	Cured
12615	3.0			+	11	n.a.	Cured
12594r	3.0			+	7	n.a.	Cured
12610r	3.0			+	4	n.a.	Cured
12622r	3.0			+	7	n.a.	Cured
12603	12.0			+	11	n.a.	Cured
12623	12.0			+	10	n.a.	Cured
12624	12.0			+	9	n.a.	Cured

TABLE 3

DETAILED ACTIVITY OF WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12504	20.0	1	11	2	0.2	<0.01	0	0	0	0	0	0
12517	20.0	4	19	6	1	<0.01	<0.01	<0.01	<0.01	<0.01	0.4	0.7
12513	20.0	3	14	1	0.2	<0.01	0	0	0	0	0	<0.01

TABLE 4

SUMMARY OF THE ACTIVITY OF WR 1544BM (AR 20613), CHLOROQUINE, AGAINST INFECTIONS OF THE AMRU-1 (CQR) STRAIN OF *PLASMODIUM VIVAX*

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12504	20.0			+	5	11	
12513	20.0			+	5	7	
12517	20.0		+		n.a.	n.a.	

TABLE 5

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12519	0.11	3	14	12	34	5	6	3	1	5	Re-Rx, higher dose	
84027	0.11	4	12	15	44	22	16	18	11	3	7	2 Re-Rx
85033	0.11	0.5	0.6	1	1	1	9	4	7	9	Re-Rx, higher dose	
12588	0.33	6	10	14	37	23	18	9	8	0.7	2	1 Re-Rx
85021	0.33	2	13	26	26	19	12	6	2	0.9	0.3	0.5 Re-Rx
88038	0.33	3	22	25	48	23	19	12	3	1	1	2 Re-Rx
12519r	0.33	14	5	0.9	3	1	0.9	<0.01	<0.01	<0.01	<0.01	0
84027r	0.33	1	1	0.7	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01 Re-Rx
85033r	0.33	7	9	8	5	3	4	1	2	0.5	0.6	0.5 Re-Rx
12589	1.0	3	17	22	28	14	12	1	0.6	<0.01	<0.01	0
86040	1.0	2	13	31	18	11	20	3	0.4	<0.01	<0.01	0
86085	1.0	1	10	6	18	13	1	<0.01	0	0	0	0
12588r	1.0	0.4	0.1	0.3	<0.01	<0.01	<0.01	<0.01	0	0	0	0
88038r	1.0	0.3	0.7	0.2	0.1	<0.01	<0.01	<0.01	0	0	0	0
85021r	1.0	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0	0
84027rr	1.0	<0.01	<0.01	0	0	0	0	0	0	0	0	0
85033rr	1.0	0.2	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0
86040r	3.0	<0.01	<0.01	0	0	<0.01	<0.01	<0.01	0	0	0	0
12589r	3.0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0
86085r	3.0	0	0	0	0	0	0	0	0	0	0	0
88038rr	3.0	0	0	0	0	0	0	0	0	0	0	0

TABLE 6

SUMMARY OF THE ACTIVITY OF WR 238605AJ (BM 12562)
AGAINST INFECTIONS OF THE AMRU-1 (CQR) STRAIN OF
PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12519	0.11	+			n.a.	n.a.	Re-Rx, higher dose
84027	0.11	+			n.a.	n.a.	Re-Rx, higher dose
85033	0.11		+		n.a.	n.a.	Re-Rx, higher dose
12588	0.33	+			n.a.	n.a.	Re-Rx, higher dose
85021	0.33		+		n.a.	n.a.	Re-Rx, higher dose
88038	0.33		+		n.a.	n.a.	Re-Rx, higher dose
12519r	0.33			+	10		Cured
84027r	0.33		+		n.a.	n.a.	Re-Rx, higher dose
85033r	0.33		+		n.a.	n.a.	Re-Rx, higher dose
12589	1.0			+	10	15	Re-Rx, higher dose
86040	1.0			+	10	10	Re-Rx, higher dose
86085	1.0			+	7	25	Re-Rx, higher dose
12588r	1.0			+	7	n.a.	Cured
88038r	1.0			+	7	13	Re-Rx, higher dose
85021r	1.0			+	4	n.a.	Cured
84027rr	1.0			+	1	n.a.	Cured
85033rr	1.0			+	6	n.a.	Cured
86040r	3.0			+	7	n.a.	Cured
12589r	3.0			+	7	n.a.	Cured
86085r	3.0			+	1	n.a.	Cured
88038rr	3.0			+	1	n.a.	Cured

TABLE 7

DETAILED SUMMARY OF THE ACTIVITY OF WR 2975AW (BJ 08241), PRIMAQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11651	0.33	1	3	6	19	4	11	10	1	2	Re-Rx, higher dose	
25057	0.33	0.6	2	2	7	13	13	4	6	6	Re-Rx, higher dose	
89022	0.33	0.7	1	5	9	3	3	1	2	0.4	0.2	0.01
86067	1.0	1	5	7	11	6	9	10	22	3	6	2
87012	1.0	1	9	20	16	25	12	7	14	8	Re-Rx, higher dose	
87027	1.0	0.8	3	9	14	20	8	2	8	9	Re-Rx, higher dose	
11651r	1.0	2	2	1	0.3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0
85057r	1.0	6	6	2	0.7	<0.01	<0.01	0	Died, fight wounds			
89022r	1.0	0.1	0.07	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0
86023	3.0	0.8	4	9	6	1	0.1	<0.01	<0.01	<0.01	<0.01	<0.01
86045	3.0	1	11	18	9	10	0.4	<0.01	<0.01	<0.01	<0.01	0.2
86071	3.0	1	6	13	8	6	0.5	<0.01	0	0	0	0
86067r	3.0	3	1	0.5	0.01	<0.01	<0.01	<0.01	0	0	0	0
87012r	3.0	14	8	2	0.9	<0.01	<0.01	<0.01	<0.01	0	0	0
87027r	3.0	8	10	7	5	0.5	<0.01	<0.01	0	0	0	0
89022rr	3.0	<0.01	<0.01	0	0	0	0	0	0	0	0	0
85070	10.0	1	16	29	9	1	0.1	<0.01	0	0	0	0
89034	10.0	0.7	4	12	1	<0.01	<0.01	0	0	0	0	0
89058	10.0	2	18	10	5	0.4	<0.01	0	0	0	0	0
86023r	10.0	0.2	0.8	0.7	0.2	<0.01	<0.01	0	0	0	0	0
86045r	10.0	0.7	3	1	2	0.1	<0.01	<0.01	0	0	0	0
86071r	10.0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0

TABLE 7 (CONT'D)

DETAILED SUMMARY OF THE ACTIVITY OF WR 2975AW (BJ 08241), PRIMAQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
87012rr	10.0	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0	0
87027rr	10.0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0
87025	30.0	0.8	4	8	0.3	<0.01	<0.01	0	0	0	0	0
87055	30.0	0.2	0.2	0.2	<0.01	<0.01	0	0	0	0	0	0
89014	30.0	1	5	11	1	0.3	<0.01	<0.01	0	0	0	0
85070r	30.0	<0.01	0.6	3	1	0.5	<0.01	<0.01	0	0	0	0
89034r	30.0	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0
89058r	30.0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0
86045rr	30.0	1	2	2	1	0.05	0	0	0	0	0	0
89014r	90.0	0	0	0	0	0	0	0	0	0	0	0

TABLE 8

SUMMARY OF THE ACIVITY OF WR 2975AW (BJ 08241), PRIMAQUINE, AGAINST INFECTIONS OF THE AMRU-1 (CQR) STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
11651	0.33		+		n.a.	n.a.	Re-Rx, higher dose
85057	0.33		+		n.a.	n.a.	Re-Rx, higher dose
89022	0.33		+		n.a.	n.a.	Re-Rx, higher dose
86067	1.0		+		n.a.	n.a.	Re-Rx, higher dose
87012	1.0		±		n.a.	n.a.	Re-Rx, higher dose
87027	1.0		±		n.a.	n.a.	Re-Rx, higher dose
11651r	1.0			+	10	n.a.	Died 21 days Post-Rx a
85057r	1.0	n.a.			n.a.	n.a.	Died day 3 Post Rx b
89022r	1.0			+	9	9	Re-Rx, higher dose
86023	3.0		+		n.a.	n.a.	Re-Rx, higher dose
86045	3.0		+		n.a.	n.a.	Re-Rx, higher dose
86071	3.0			+	7	10	Re-Rx, higher dose
86067r	3.0			+	7	n.a.	Cured
87012r	3.0			+	8	11	Re-Rx, higher dose
87027r	3.0			+	7	13	Re-Rx, higher dose
89022rr	3.0			+	1	n.a.	Cured

a. Encephalitis
b. Fight wounds

TABLE 8 (CONT'D)

SUMMARY OF THE ACTIVITY OF WR 2975AW (BJ 08241), PRIMAQUINE, AGAINST INFECTIONS OF THE AMRU-1 (CQR) STRAIN OF P. VIVAX (CONT'D)

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
85070	10.0			+	7	18	Re-Rx, higher dose
89034	10.0			+	6	18	Re-Rx, higher dose
89058	10.0			+	7	18	Re-Rx, higher dose
86023r	10.0			+	6	n.a.	Cured
86045r	10.0			+	7		Re-Rx, higher dose
86071r	10.0			+	7	82	
87012rr	10.0			+	4	n.a.	Cured
87027rr	10.0			+	6		
87025	30.0			+	6	n.a.	Cured
87055	30.0			+	5	n.a.	Cured
89014	30.0			+	7	25	Re-Rx, higher dose
85070r	30.0			+	7	n.a.	Cured
89034r	30.0			+	6	n.a.	Cured
89058r	30.0			+	6	n.a.	Cured
86045rr	30.0						
89014	90.0			+	1	n.a.	Cured

TABLE 9

DETAILED ACTIVITY OF WR 1544BM(AR 20613), CHLOROQUINE AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12683	10.0	3	14	26	11	6	0.6	1	2	12	15	14
12690	10.0	3	7	23	3	1	0.5	1	3	10	13	2
12722	10.0	0.3	0.4	1	<0.01	<0.01	0.3	0.4	1	<0.01	<0.01	<0.01

TABLE 10

SUMMARY OF THE ACTIVITY OF WR 1544BM (AR 20613), CHLOROQUINE AGAINST PLASMODIUM VIVAX (AMRU-1 STRAIN) INFECTIONS

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12683	10.0		±				
12690	10.0		±				
12722	10.0*		+				

* aberrant inoculation

TABLE 11

DETAILED ACTIVITY OF WR 2975AW (BJ 0824), PRIMAQUINE, ALONE AND IN COMBINATION WITH WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12699	1.0(a)	11	12	49	42	26	26	25	Re-Rx, combination			
12700	1.0(a)	2	8	24	26	17	20	21	Re-Rx, combination			
12701	1.0(a)	2	7	26	34	23	15	32	Re-Rx, combination			
12685	1.0(a) 10.0(b)	1	4	13	9	5	2	4	5	8	47	Re-Rx
12713	1.0(a) 10.0(b)	2	11	12	15	2	0.2	<0.01	<0.01	0.3	0.7	Re-Rx
12714	1.0(a) 10.0(b)	1	7	6	2	0.6	<0.01	<0.01	<0.01	0.3	2	Re-Rx
12699r	1.0(a) 10.0(b)	26	25	7	2	0.2	0.3	<0.01	0.2	<0.01	<0.01	<0.01
12700r	1.0(a) 10.0(b)	20	21	24	0.5	0.1	<0.01	<0.01	<0.01	<0.01	0	0
12701r	1.0(a) 10.0(b)	15	32	18	9	1	0.2	0.3	<0.01	0.4	0.2	0.3
12685r	3.0(a) 10.0(b)	47	15	4	2	<0.01	<0.01	0	0	0	<0.01	0.01
12713r	3.0(a) 10.0(b)	0.7	1	0.5	0.1	<0.01	0	0	0	0	0	0
12714r	3.0(a) 10.0(b)	2	2	3	1	<0.01	<0.01	0	0	0	<0.01	<0.01

(a) Primaquine (b) Chloroquine

TABLE 11 (CONT'D)

DETAILED ACTIVITY OF WR 2975AW (BJ 0824), PRIMAQUINE, ALONE AND IN COMBINATION WITH WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12699rr	3.0(a) 10.0(b)	<0.01	<0.01	0	0	0	0	0	0	0	0	0
12701rr	3.0(a) 10.0(b)	1	0.5	0.9	<0.01	<0.01	0	0	0	0	0	0
12685rr	10.0(a) 10.0(b)	<0.01	<0.01	0	0	0	0	0	0	0	0	0
12713rr	10.0(a) 10.0(b)	0	<0.01	0	<0.01	0	0	0	0	0	0	0
12714rr	10.0(a) 10.0(b)	<0.01	<0.01	<0.01	0	0	0	0	0	0	0	0

a. Primaquine
b Chloroquine

TABLE 12

SUMMARY OF THE ACTIVITY OF WR 2975AW (BJ 0824), PRIMAQUINE, ALONE AND IN COMBINATION WITH WR 1544BM (AR 20613), CHLOROQUINE, AGAINST PLASMODIUM VIVAX (AMRU-1) INFECTIONS

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
12699	1.0(a)	+			n.a.	n.a.	Re-Rx, combination
12700	1.0(a)	+			n.a.	n.a.	Re-Rx, combination
12701	1.0(a)	+			n.a.	n.a.	Re-Rx, combination
12685	1.0(a)		+		n.a.	n.a.	Re-Rx, higher dose
	10.0(b)						
12713	1.0(a)		+		n.a.	n.a.	Re-Rx, higher dose
	10.0(b)						
12714	1.0(a)		+		n.a.	n.a.	Re-Rx, higher dose
	10.0(b)						
12699r	1.0(a)						
	10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12700r	1.0(a)						
	10.0(b)			+	9	12	
12701r	1.0(a)						
	10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose

a. Primaquine
b. Chloroquine

TABLE 12

SUMMARY OF THE ACTIVITY OF WR 2975AW (BJ 0824), PRIMAQUINE, ALONE AND IN COMBINATION WITH WR 1544BM (AR 20613), CHLOROQUINE, AGAINST PLASMODIUM VIVAX (AMRU-1) INFECTIONS (CONT'D)

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
12685r	3.0(a) 10.0(b)			+	6	6	Re-Rx, higher dose
12713r	3.0(a) 10.0(b)			+	5	14	Re-Rx, higher dose
12714r	3.0(a) 10.0(b)			+	6	6	Re-Rx, higher dose
L2699rr	3.0(a) 10.0(b)			+	1	n.a.	Cured
L2701rr	3.0(a) 10.0(b)			+	5	n.a.	Cured
L2685rr	10.0(a) 10.0(b)			+	2	n.a.	Cured
L2713rr	10.0(a) 10.0(b)			+	4	n.a.	Cured
L2714rr	10.0(a) 10.0(b)			+	3	n.a.	Cured

a. Primaquine
b. Chloroquine

TABLE 13

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12628	0.1	2	5	21	20	5	27	17	Re-Rx, combination			
12704	0.1	2	6	19	30	29	36	25	Re-Rx, combination			
12711	0.1	2	20	23	19	27	23	34	Re-Rx, combination			
12629	0.3	2	5	15	25	12	10	2	Re-Rx, combination			
12703	0.3	3	12	32	42	28	22	28	Re-Rx, combination			
12705	0.3	2	9	24	36	27	2	11	Re-Rx, combination			
12674	1.0	4	11	12	47	11	1	<0.01	<0.01	<0.01	<0.01	0
12706	1.0	3	12	21	26	7	18	<0.01	Died, Klebsiella			
12715	1.0	1	6	6	31	11	14	0.3	<0.01	<0.01	<0.01	0

TABLE 14

SUMMARY OF THE ACTIVITY OF WR 238605AJ (BM 12562)
AGAINST PLASMODIUM VIVAX (AMRU-1) INFECTIONS

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
12628	0.1	+			n.a.	n.a.	Re-Rx, combination
12704	0.1	+			n.a.	n.a.	Re-Rx, combination
12711	0.1	+			n.a.	n.a.	Re-Rx, combination
12629	0.3	+			n.a.	n.a.	Re-Rx, combination
12703	0.3	+			n.a.	n.a.	Re-Rx, combination
12705	0.3	+			n.a.	n.a.	Re-Rx, combination
12674	1.0			+	10	25	Re-Rx, combination
12706	1.0				n.a.	n.a.	Died Day 3 Post Rx*
12715	1.0			+	10	21	Re-Rx, combination

* Intercurrent Infection

TABLE 15

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12719	0.1(a) 10.0(b)	2	12	17	19	2	1	1	3	4	5	1
12720	0.1(a) 10.0(b)	3	12	16	14	9	3	2	2	1	2	2
12721	0.1(a) 10.0(b)	2	16	6	9	4	<0.01	0.2	0.5	0.3	0.5	0.5
12628r	0.1(a) 10.0(b)	27	17	18	7	6	3	2	2	0.6	0.3	0.5
12704r	0.1(a) 10.0(b)	36	25	32	14	4	1	0.7	0.6	0.6	0.6	0.5
12711r	0.1(a) 10.0(b)	23	34	17	20	6	2	0.5	0.1	<0.01	<0.01	<0.01
12668	0.3(a) 10.0(b)	3	13	20	18	12	0.7	0.2	<0.01	<0.01	<0.01	0
12718	0.3(a) 10.0(b)	0.4	2	0.6	0.2	<0.01	<0.01	0	0	0	0	0
12723	0.3(a) 10.0(b)	2	16	16	4	2	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
12629r	0.3(a) 10.0(b)	10	2	0.2	<0.01	<0.01	0	0	0	0	0	0
12703r	0.3(a) 10.0(b)	22	28	9	2	0.3	<0.01	<0.01	<0.01	<0.01	0	0
12705r	0.3(a) 10.0(b)	2	11	7	0.5	0.4	<0.01	<0.01	<0.01	<0.01	0	0

(a) WR 238605 (b) Chloroquine

TABLE 15 (CONT'D)

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12717	1.0(a) 10.0(b)	3	12	21	25	4	0.2	<0.01	<0.01	0	0	0
12684	1.0(a) 10.0(b)	2	17	12	31	9	0.8	0.3	<0.01	<0.01	<0.01	0
12724	1.0(a) 10.0(b)	1	8	6	2	0.2	<0.01	<0.01	0	0	0	0
12719r	1.0(a) 10.0(b)	5	1	0.3	<0.01	<0.01	0	0	0	0	0	0
12720r	1.0(a) 10.0(b)	2	2	0.7	0.7	<0.01	<0.01	<0.01	0	0	0	0
12721r	1.0(a) 10.0(b)	0.5	0.5	0.3	<0.01	<0.01	0	0	0	0	0	0
12628rr	1.0(a) 10.0(b)	0.6	1	1	0.3	<0.01	<0.01	<0.01	<0.01	<0.01	0	0
12629rr	1.0(a) 10.0(b)	<0.01	<0.01	0	0	0	0	0	0	0	0	0
12668r	1.0(a) 10.0(b)	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0	0
12674r	1.0(a) 10.0(b)	<0.01	<0.01	<0.01	0	0	0	0	0	0	0	0
12703rr	1.0(a) 10.0(b)	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0	0
12704r	1.0(a) 10.0(b)	0.4	0.4	<0.01	<0.01	0	0	0	0	0	0	0

(a) WR 238605 (b) Chloroquine

TABLE 15 (CONT'D)

DETAILED ACTIVITY OF WR 238605AJ (BM 12562) PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST AMRU-1 STRAIN INFECTIONS OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12711rr	1.0(a) 10.0(b)	<0.01	<0.01	<0.01	0	0	0	0	0	0	0	0
12715r	1.0(a) 10.0(b)	<0.01	<0.01	0	0	0	0	0	0	0	0	0
12718r	1.0(a) 10.0(b)	<0.01	<0.01	0	0	0	0	0	0	0	0	0
12723r	1.0(a) 10.0(b)	<0.01	0	<0.01	<0.01	0	0	0	0	0	0	0
12684r	3.0(a) 10.0(b)	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0	0	0

(a) WR 238605
(b) Chloroquine

TABLE 16

SUMMARY OF THE ACTIVITY OF WR 238605AJ (BM 12562) PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST INFECTIONS OF PLASMODIUM VIVAX (AMRU-1)

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12719	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12720	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12721	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12628r	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12704r	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12711r	0.1(a) 10.0(b)		+		n.a.	n.a.	Re-Rx, higher dose
12668	0.3(a) 10.0(b)			+	10	23	Re-Rx, higher dose
12718	0.3(a) 10.0(b)			+	6	20	Re-Rx, higher dose
12723	0.3(a) 10.0(b)			+	11	13	Re-Rx, higher dose

a. WR 238605
b. Chloroquine

TABLE 16 (CONT'D)

SUMMARY OF THE ACTIVITY OF WR 238605AJ (BM 12562)
PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST INFECTIONS
OF PLASMODIUM VIVAX (AMRU-1)

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12629r	0.3(a) 10.0(b)			+	4	8	Re-Rx, higher dose
12703r	0.3(a) 10.0(b)			+	9	22	Re-Rx, higher dose
12705r	0.3(a) 10.0(b)			+	9	n.a.	Cured
12717	1.0(a) 10.0(b)			+	8	n.a.	Cured
12684	1.0(a) 10.0(b)			+	10	33	Re-Rx, higher dose
12724	1.0(a) 10.0(b)			+	7	n.a.	Cured
12719r	1.0(a) 10.0(b)			+	5	n.a.	Cured
12720r	1.0(a) 10.0(b)			+	7	n.a.	*
12721r	1.0(a) 10.0(b)			+	5	n.a.	Cured
12628rr	1.0(a) 10.0(b)			+	9	n.a.	Cured
12629rr	1.0(a)			+	2	n.a.	Cured

a) WR 238605 b) chloroquine
* Died Day 25 Post-Rx, intercurrent infection

TABLE 16 (CONT'D)

SUMMARY OF THE ACTIVITY OF WR 238605AJ (BM 12562)
PLUS WR 1544BM (AR 20613), CHLOROQUINE, AGAINST INFECTIONS
OF PLASMODIUM VIVAX (AMRU-1)

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
12668r	1.0(a) 10.0(b)			+	4	n.a.	Cured
12674r	1.0(a) 10.0(b)			+	4	n.a.	Cured
12703rr	1.0(a) 10.0(b)			+	4	n.a.	Cured
12704rr	1.0(a) 10.0(b)			+	4	n.a.	Cured
12711rr	1.0(a) 10.0(b)			+	3	n.a.	Cured
12715r	1.0(a) 10.0(b)			+	1	n.a.	Cured
12718r	1.0(a) 10.0(b)			+	2	n.a.	Cured
12713r	1.0(a) 10.0(b)			+	4	n.a.	Cured
12684r	3.0(a) 10.0(b)			+	4	n.a.	Cured

a WR 238605 b Chloroquine

TABLE 17

SUMMARY OF DRUG ACTIVITIES, ALONE AND IN COMBINATION, AGAINST *PLASMODIUM VIVAX* INFECTIONS

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
AMRU-1								
			WR 1544BM - Chloroquine					
	30.0	10.0	0/3	0/3			0/3	0/3
	60.0	20.0	2/3	0/3			2/3	0/3
			WR 2975AW - Primaquine					
	0.99	0.33	0/3	0/3			0/3	0/3
	3.0	1.0	0/6	0/6	2/2	0/1	2/6	0/7
	9.0	3.0	1/3	0/3	4/4	3/4	5/7	2/7
	30.0	10.0	3/3	0/3	5/5	3/5	8/8	5/8
	90.0	30.0	3/3	2/3	4/4	4/4	7/7	6/7
	270.0	90.0	1/1	1/1			1/1	1/1
	WR 2975AW, primaquine(a) plus WR 1544BM, chloroquine(b)							
	3.0(a) 1.0(a) 30.0(b) 10.0(b)		0/3	0/3	1/3	0/3	1/6	0/6
	9.0(a) 3.0(a) 30.0(b) 10.0(b)				5/5	2/5	5/5	2/5
	30.0(a) 10.0(a) 30.0(b) 10.0(b)				3/3	3/3	3/3	3/3
			WR 238605AJ					
	0.33	0.11	0/6	0/6			0/6	0/6
	0.99	0.33	0/6	0/6	1/3	1/3	1/9	1/9
	3.0	1.0	5/5	0/5	5/5	4/5	5/10	4/10
	9.0	3.0		4/4	4/4	4/4	4/4	4/4

TABLE 17 (CONT'D)

SUMMARY OF DRUG ACTIVITIES, ALONE AND IN COMBINATION, AGAINST PLASMODIUM VIVAX INFECTIONS

MALARIA STRAIN	DOSE mg/kg TOTAL	DOSE mg/kg DAILY	PRIMARY TREATMENTS CLEARED	PRIMARY TREATMENTS CURED	REPEAT TREATMENTS CLEARED	REPEAT TREATMENTS CURED	TOTAL TREATMENTS CLEARED	TOTAL TREATMENTS CURED
AMRU-1								
WR 2975AW, primaquine(a) plus WR 1544BM, chloroquine (b)								
	0.3(a) 30.0(b)	0.1(a) 10.0(b)	0/3	0/3	0/3	0/3	0/6	0/6
	0.9(a) 30.0(b)	0.3(a) 10.0(b)	3/3	0/3	3/3	1/3	6/6	1/6
	30.0(a) 30.0(a)	1.0(a) 10.0(b)	3/3	1/3	13/13	12/12	16/16	13/15
	9.0(a) 30.0(b)	3.0(a) 10.0(b)			1/1	1/1	1/1	1/1

TABLE 18

CHALLENGE (10^4 TROPHOZOITES) WITH THE FVO STRAIN OF *PLASMODIUM FALCIPARUM*

MONK. NO.	PRE-PATENT (Days)	MAXIMUM PARASITEMIA PER CMM	PATENT DAY	NOTES
		MALARIA NAIVE		
12738	9	440,000	6	Rx, mefloquine
12739	8	763,000	7	Rx, mefloquine
12740	9	270,000	6	Rx, mefloquine
		CURED OF ONE FVO INFECTION (a)		
12687	13	119,000	6	Rx,mefloquine, died 25 days post Rx,inter-current infec-tion
12727	15	222,000	8	Rx,mefloquine,
		VACCINATED, MALARIA NAIVE (b)		
12726	8	542,000	7	Rx,mefloquine, died, day 1 post Rx, malaria
12730	8	1,232,000	8	Rx,mefloquine
12731	8	1,277,000	8	Rx,mefloquine, died of malaria after 2 days of treatment

(a) Four months prior to rechallenge

(b) See text

TABLE 19

SPOROZOITE-INDUCED INFECTIONS OF THE

SANTA LUCIA STRAIN OF *PLASMODIUM FALCIPARUM*

IN *AOTUS L. LEMURINUS*

MONK. NO.	PREPATENT PD. (DAYS)	MAXIMUM PARASITEMIA PER CMM ($\times 10^3$)
	GROUP 1 - Splenectomized prior to inoculation	
12733	23	> 35
12734	21	19
12736		
12737		
	GROUP 2 - Splenectomized day 7 post inoculation	
12716	21	494
12741	29 (one day only)	
12743	23	> 72
12753	29	< 0.01
	GROUP 3 - Still intact	
12746		
12747	23	> 77
12750	Positive day 25 only	
12751		

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 7 Feb 97

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Contract Number DAMD17-91-C-1072. Request the limited distribution statement for Accession Document Numbers ADB214740, ADB198405, ADB210896, ADB183789, and ADB173254 be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Mrs. Judy Pawlus at DSN 343-7322.

FOR THE COMMANDER:

GARY R. GILBERT
Colonel, MS
Deputy Chief of Staff for
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